initiated by mixing the two solutions by using the stopped-flow device, and the decrease in the absorbance of the solution at 296 nm with time was then recorded on a storage oscilloscope. With the methoxide concentrations used (0.001–0.003 M) two consecutive reactions were observed. The first of these is the reaction of CH_3O^- with **1** to form **2a**; the second is the CH_3O^--promoted decomposition of **2a**. As long as the Me_2SO content of the solvent medium was 80% or greater the equilibrium constant for the first reaction was large enough, and its rate was fast enough compared to the rate of the second reaction, so that one could determine the value of the absorbance associated with the completion of the $1 + CH_3O^- \rightleftarrows$ **2a** reaction (A_∞^{init}) quite accurately. For solutions containing less than 80% Me_2SO this was no longer true.

Measurement of k_{-MeO}. A solution of a 1:1 buffer of either chloroacetic acid–sodium chloroacetate or formic acid–sodium formate in Me_2SO–methanol having the appropriate methanol content was placed in one of the reservoir syringes of the stopped-flow spectrophotometer. A 1×10^{-4} M solution of **2a** in 95% Me_2SO–5% methanol was prepared by adding $1.2–1.4 \times 10^{-4}$ M methoxide to a 1×10^{-4} M solution of **1** in 95% Me_2SO–5% methanol, and this solution of **2a** was then immediately placed in the other reservoir syringe of the stopped-flow spectrophotometer. Upon mixing the two solutions in the stopped-flow device the absorbance at 296 nm was observed to increase due to the regeneration of **1**. The rate of regeneration of **1** from **2a** was determined from the slope of a plot of log $(A_\infty - A)$ vs. time.

Products of the Decomposition of 1 in the Presence of Excess Sodium Methoxide. To 0.248 g (1.0 mmol) of **1** in 10 mL of Me_2SO was added 1.0 mL of 2.4 M CH_3ONa in methanol, and the solution was allowed to stand for 15 min. Water (5 mL) was then added, and the solvents were removed by evaporation under an oil pump vacuum at a temperature of 35–40 °C. The residue was treated with a little methanol and filtered, and the methanol was removed under reduced pressure. The resulting residue was insoluble in benzene but quite soluble in water. A portion of the residue was dissolved in methanol and several milliliters of benzene was added to the methanol solution. This led to the precipitation of a quite hygroscopic solid whose IR spectrum showed strong bands at 1010 and 960 cm^{-1} [as would be expected for a sulfinate ion (SO_2^-) functionality] but no absorption bands in either of the regions where sulfonyl groups have strong absorption. The remainder of the residue was dissolved in 10 mL of water, and 8 mL of 1 N hydrochloric acid was added. A white solid precipitated almost immediately. The resulting suspension was extracted several times with chloroform–benzene, the extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure; TLC of the residue showed that it was an approximately equimolar mixture of **1** and the corresponding thiolsulfinate **4**, dibenzo[*ce*]-1,2-dithiin 1-oxide,[16]

Acknowledgment. The support of this research by the Robert A. Welch Foundation (Grant D-650) is gratefully acknowledged.

Registry No. 1, 25331-82-2; **2a**, 84810-85-5; methoxide ion, 3315-60-4.

(16) Boduszek, B.; Kice, J. L. *J. Org. Chem.* **1982**, *47*, 3199.

Synthesis of an Alleged Constituent of New Brunswick Cranberry Leaves: The So-Called Cannivonine

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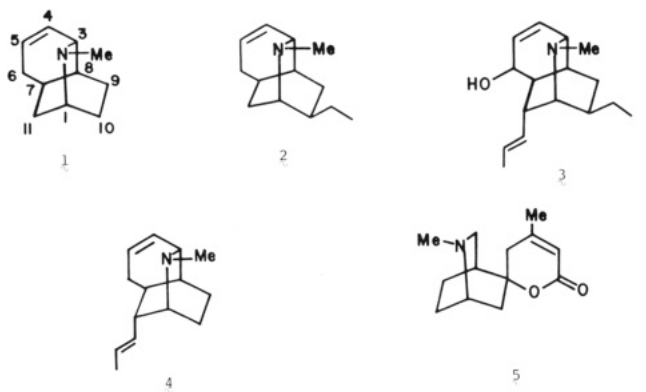
An unambiguous ten-step synthesis of the compound possessing the reputed structure of the cranberry alkaloid cannivonine (**1**) is presented. Stereoselective reductive amination of the known *cis*-$\Delta^{5,6}$-2-octalone, protection of the nitrogen substituent, epoxidation, and N-deprotection with concomitant transannular ring closure provide a product possessing the desired 2-azatricyclo[5.3.1.$0^{3,8}$]undecane skeleton. Subsequent dehydration then yields the alleged cannivonine. Since the spectral data of the synthetic material fail to match those reported for cannivonine, a complete reinterpretation of the published data (and probably reisolation as well) and a reassignment of the structure of cannivonine appear to be in order.

Extracts from cranberry leaves (especially European) have found application in "naive" cancer therapy as well as traditional folklore medicine. In 1971, Jankowski and co-workers began a study into the basic constituents of extracts of cranberry leaves (*Viccinium oxycoccus*) native to New Brunswick. Their efforts resulted in a series of disclosures detailing the isolation and characterization of *N*-methylindolic and *N*-methylazatricyclic alkaloids believed to be the physiologically active ingredients of this plant.[1]

Of a minimum of 19 different basic substances detected by thin-layer chromatography, the structures of 8 of the alkaloids have thus far been communicated, 4 from the indole family, the cannagunine series, and 4 from the azatricyclic family, the cannivonine series (**1–4**). Unlike the four indole alkaloids, the cannivonines are a biogenetically interesting group because of their heretofore unknown 2-azatricyclo[5.3.1.$0^{3,8}$]undecane skeleton. Their architectural similarity to dioscorine (**5**), a natural product of known biogenetic origin, has, however, been alluded to.[2]



1 2 3 4 5

(1) (a) Jankowski, K.; Boudreau, J.; Jankowska, I. *Experentia* **1971**, *27*, 1141. (b) Jankowski, K.; Jankowska, I. *Ibid.* **1971**, *27*, 1383. (c) Jankowski, K. *Ibid.* **1973**, *29*, 519. (d) Jankowski, K. *Ibid.* **1973**, *29*, 1334. (e) Jankowski, K.; Godin, S.; Cundasawmy, N. E. *Can. J. Chem.* **1974**, *52*, 2064.

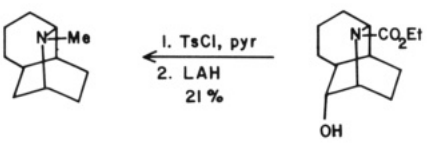
(2) Snieckus, V. A. "The Alkaloids-Specialist Periodical Reports"; The Chemical Society: Burlington House, London, 1973; Vol. 3, p 323.

0022-3263/83/1948-1000$01.50/0

The structure of compound **1**, the first and simplest member of the azatricyclic group, named cannivonine by Jankowski, was proposed on the basis of spectroscopic and chemical degradative evidence.[1b] In addition to mass spectral data (including the molecular ion 163) and an elemental analysis corresponding to the proposed structure, the IR spectrum of cannivonine revealed the presence of a double bond stretching vibration at 1620 cm^{-1} and the absence of NH absorption. The ^1H NMR (T-60, $CDCl_3$, δ) displayed two olefinic protons (5.3), five protons α to the nitrogen atom (3.7–2.3), an *N*-methyl singlet (3.3), and three allylic protons (2.3–2.0). A series of chemical degradations were carried out and these studies used to further support the assigned structure.[1b,3]

The remaining three azatricycles (**2**–**4**) were found by Jankowski to be the principal constituents of the basic fraction of the cranberry extracts.[1d] The proposed structure and stereochemistry of compound **3** (named cannivonine 2) relied heavily on the analysis of a 220-MHz ^1H NMR spectrum coupled with europium shift reagent studies.

Subsequent to these structural elucidation studies, Jankowski reported a synthesis of the skeletal "dihydrocannivonine" **7**.[4] Assignment of structures to this

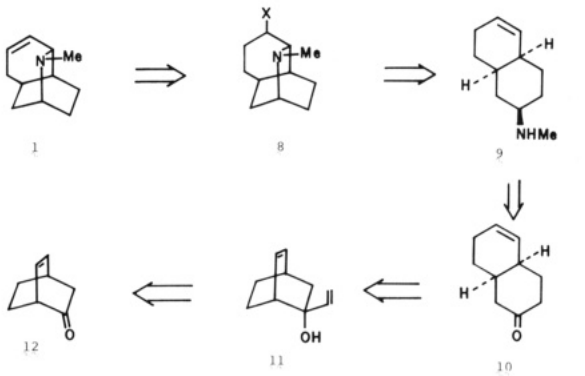


7 6

material and its progenitors was based on analysis of ^1H NMR, ^{13}C NMR, and mass spectral data. Surprisingly, Jankowski made no mention of any attempts to confirm the proposed structure of natural cannivonine (**1**) by correlating this compound with his synthetic "dihydrocannivonine" **7** through the obvious hydrogenation experiment. This peculiarity was only one of several disturbing points that surfaced on careful reading of the published series of structure papers on the cannivonine alkaloids.[5,6] Other anamolies include the following items: (i) the indication that a total of three azatricyclic alkaloids had been isolated, yet four compounds (**1**–**4**) were reported in the literature; (ii) the claim that oxidative degradation of cannivonine (**1**) produces a Bredt-rule-violating diene; (iii) the puzzling result that cannivonine 2 (**3**) is deuterated at C3, C6, C11, and C3′ when employing "Djerassi's classic method" (sodium methoxide, [*hydroxyl*-^2H]methanol, and heavy water at reflux); (iv) the fact that the stereostructures of cannivonines 1 and 3 were rapidly assigned on the basis of what would appear to be inconclusive evidence.

Since the structural characterization of the cannivonines (including the purported synthesis of dihydrocannivonine) provoked considerable suspicion, an unambiguous synthesis of the simplest member, **1**, appeared crucial to confirming the identity or misassignment of the azatricyclic alkaloids.[7,8] Moreover, the biogenetic intrigue surrounding

Scheme I. Retrosynthetic Analysis of Cannivonine



1 8 9 10 11 12

these rare isoquinuclidine structures provided additional motivation for undertaking this synthetic endeavor.

Synthetic Analysis

In planning a synthesis of **1**, particular attention had to be given to the fact that its bridgehead nitrogen was capable of participating in skeletal rearrangements. Concern over this point was apparently not without reason, for the purported synthesis of dihydrocannivonine **7** by Jankowski was troubled by an inferior overall yield of 0.5% for the seven-step sequence. His strategy utilized Cava's Diels-Alder method for isoquinuclidine synthesis[9] and consequently produced the A ring last via a C–C bond-forming process. Skeletal reorganization through an aziridinium intermediate appeared likely during the final stages of Jankowski's synthesis, which involved removal of the superfluous hydroxyl group by conversion to its tosylate followed by lithium aluminum hydride reduction (**6** → **7**).

With the aforementioned information in mind, it appeared more reasonable to construct the isoquinuclidine nucleus last and then to introduce the C4–C5 unsaturation under conditions that would preclude skeletal rearrangement by nitrogen participation. The retrosynthetic analysis displayed in Scheme I thus emerged.

The proximity of the functional group X on the A ring of **8** to the bridgehead nitrogen suggested the possibility of a strategic C3–N disconnection. In fact, a Dreiding model of β-aminodecalin (**9**), the simplified structure resulting from such a disconnection, revealed the existence of a stereoelectronically favorable intramolecular transdiaxial opening by nitrogen nucleophile on a potential onium or epoxide intermediate. It was also reasoned that the transannular cyclization of **9** could be promoted by the complexation of a metal to the olefin. Aminometalations with Hg(II) and Pd(II) have recently received considerable attention,[10] but none have been successfully carried out on a system resembling that at hand. Particularly noteworthy in this context though was Trost's π-allylpalladium route to ibogamine.[10f] While the palladium-induced addition of amines to cyclohexenes and to cis-2-olefins has been studied, these reactions generally prove quite sluggish

(3) (a) Dickel, D. F.; Holden, C. L.; Maxfield, R. C.; Paszek, L. E.; Taylor, W. I. *J. Am. Chem. Soc.* **1958**, *80*, 123. (b) Schenker, K.; Druey, J. *Helv. Chim. Acta* **1959**, *42*, 1971. (c) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnett, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1965**, *87*, 2073; **1966**, *88*, 3099.

(4) Jankowski, K. *Tetrahedron Lett.* **1976**, 3309.

(5) Snieckus, V. A. "The Alkaloids-Specialist Periodical Reports"; The Chemical Society: Burlington House, London, 1975; Vol. 5, p 288.

(6) Snieckus, V. A. "The Alkaloids-Specialist Periodical Reports"; The Chemical Society: Burlington House, London, 1973; Vol. 3, p 199.

(7) A preliminary account of this work has appeared: Kozikowski, A. P.; Schmiesing, R. *J. Chem. Soc., Chem. Commun.* **1979**, 106.

(8) A full paper describing the synthesis of **1** by a route related to our own has been published: Evans, D. A.; Golob, A. M.; Mandel, N. S.; Mandel, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 8170.

(9) Cava, M. P.; Wilkins, C. K., Jr.; Dalton, D. R.; Bessho, K. *J. Org. Chem.* **1965**, *30*, 3772.

(10) See, for example: (a) Perie, J.; Laval, J. P.; Roussel, J.; Lattes, A. *Tetrahedron Lett.* **1971**, 4399. (b) Åkermark, B.; Bäckvall, J. E.; Hegedus, L. S.; Zetterberg, K.; Siirala-Hansén, K.; Sjöberg, K. *J. Organomet. Chem.* **1974**, *72*, 127. (c) Hegedus, L. S.; Allen, G. F.; Waterman, W. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674. (d) Barrelle, M.; Apparu, M. *Tetrahedron Lett.* **1976**, *2611*. (e) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329. (f) Trost, B. M.; Godleski, S. A.; Genêt, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (g) Hegedus, L. S.; McKearin, J. M. *Ibid.* **1982**, *104*, 2444.

in character.[10b] Thus only a trace of cyclohexyldimethylamine was found from the reaction of cyclohexene and dimethylamine.

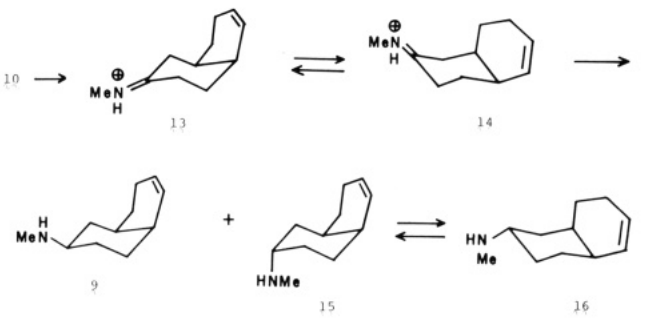
In spite of these negative reports, we felt that application of Hegedus' aminopalladation process to **9** was worthy of examination, for this chemistry if successful would provide the most efficient entry to **1**. If the aminometalation process failed, then the less direct but more secure process of epoxide formation and transannular opening could be employed to give **8** (X = OH).[11]

The aminodecalin **9** required for these studies was envisioned to arise through the stereoselective reductive amination of the known *cis*-$\Delta^{5,6}$-2-octalone (**10**), a ketone first described by Berson as the major product of the pyrolytic [3,3] sigmatropic rearrangement of the bicyclic intermediate **11**.[12] Evans' more recent low-temperature modification of this oxy-Cope process provided a synthetically more attractive route to **10**. By literature precedent, the alcoholic precursor **11** was readily available by addition of vinylmagnesium bromide to bicyclo[2.2.2]-oct-5-en-2-one.[12a] To complete the retrosynthetic analysis, ketone **12** was clearly recognized as the product of a [4 + 2] cycloaddition reaction between 1,3-cyclohexadiene and a ketene equivalent. Two independent three-step procedures have, in fact, been reported for **12**. The earlier by Hine[14] involved (i) cycloaddition between 1,3-cyclohexadiene and vinyl acetate, (ii) hydrolysis of the bicyclic acetate, and (iii) oxidation of the secondary alcohol with Jones reagent. The more recent synthesis by Freeman[15] entailed (i) cycloaddition between 1,3-cyclohexadiene and acrylonitrile, (ii) α-chlorination of the bicyclic nitrile, and (iii) hydrolysis of the α-chloronitrile with potassium hydroxide.[16]

Results and Discussion

In 1955 Alder and co-workers first described the successful Diels–Alder reaction between 1,3-cyclohexadiene and acrylonitrile.[17] On repeating this reaction in our laboratory, it was found that reproducibly high yields of **12** could be obtained if a 2:1 molar ratio of dienophile to diene was used. Chlorination of the cycloadduct according to the procedure of Freeman proved straightforward.[15] Several attempts to convert this α-chloronitrile to the ketone **12** by employing sodium sulfide nonahydrate proved unsatisfactory.[19] On the other hand, the KOH/Me_2SO method of Freeman did provide consistently high yields of the desired bicyclooctenone. In accord with earlier work,[12a] vinylmagnesium bromide reacted with **12** to deliver a 2:1 mixture of **11** and the 2-*exo*-vinyl-2-*endo*-hydroxy isomer. The isomer ratio could be improved slightly by conducting the Grignard addition reaction at lower temperatures (−78 and 0 °C). Unfortunately, this improved isomer ratio came at the expense of the isolated yield (50% vs. 84% for the room-temperature case). Since **11** was not easily separated from its isomer by conventional chromatography, the distilled mixture was carried on to the next step. We made the reasonable assumption that the wrong isomer would not interfere during the oxy-Cope rearrangement of **11** and that the rearranged ketone **10** could then be readily separated from the unrearranged alcohol.

Scheme II



Initially, the Cope reaction of the anion prepared from **11** by using potassium hydride in tetrahydrofuran was found to give inconsistent yields of **10**. After some experimentation, reproducibly high yields of **10** were achieved by conducting the rearrangement reaction in the presence of 1 equiv of the potassium-specific ionophore 18-crown-6 in dimethoxyethane as solvent at room temperature overnight. As anticipated, this ketone could be isolated completely free of the undesired endo alcohol by subjecting the crude mixture to medium-pressure liquid chromatography (MPLC).

At this stage, we needed to address the problem of reductive amination of ketone **10**. We began by examining the convenient "one-pot" procedure (CH_3NH_2·HCl/$NaCNBH_3$) developed by Borch and co-workers[20] rather than trying to prepare and isolate an imine and then subjecting this to reduction. The product amine (**9**, **15**; single spot by TLC; see Scheme II) obtained from the Borch method was readily identified on the basis of spectroscopic evidence (^1H NMR, IR, MS). Further confirmation of structure was obtained by noting that the addition of trifluoroacetic acid to the ^1H NMR sample of the amine led to a downfield shift of the *N*-methyl protons from δ 2.42 to 2.95 accompanied by a change in multiplicity from a singlet to a triplet. These observations are in accord with results described by Warnhoff[21a] and by Anderson.[21b] None of the spectral evidence available was, however, of value in answering the question of utmost concern at this point, i.e., what is the degree of stereoselectivity, if any, in the reduction of the iminium ion intermediate **13** (**14**)?[22] The cis fusion of the hexahydronaphthalenone structure suggested a possible preference for hydride attack from the convex face to give predominantly the desired β-amino group at the new stereocenter. Because of the conformational mobility of cis-decalyl derivatives in general[23] the transition state for reduction could resemble either conformer **13** or **14**, thus undermining any attempt to confidently predict the course of the reduction. Additionally,

(11) For some examples of epoxide opening by amines, see: (a) Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1974**, *39*, 3822. (b) Roush, W. *J. Am. Chem. Soc.* **1978**, *100*, 3599. (c) Glass, R. S.; Deardoff, D. R.; Gains, L. H. *Tetrahedron Lett.* **1978**, 2965. (d) Wilson, S. R.; Sawicki, R. A. *Ibid.* **1978**, 2969.

(12) (a) Berson, J. A.; Jones, M., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5018, 5019. (b) Berson, J. A.; Walsh, E. J., Jr. *Ibid.* **1968**, *90*, 4729, 4730, 4732.

(13) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(14) Hine, J.; Brown, J. A.; Zalkow, L. H.; Gardner, W. E.; Hine, M. *J. Am. Chem. Soc.* **1955**, *77*, 594.

(15) Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.* **1968**, *33*, 2211.

(16) A third type of ketene equivalent, di-*n*-butyl vinylboronate, was employed by Evans et al. in their studies.[8]

(17) Alder, K.; Krieger, H.; Weiss, H. *Chem. Ber.* **1955**, *88*, 144.

(18) Gregson, R.; Mirrington, R. *Aust. J. Chem.* **1976**, *29*, 2037.

(19) Evans, D. A.; Scott, W. L.; Truesdale, L. K. *Tetrahedron Lett.* **1972**, 121.

(20) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(21) (a) Ma, J. C. N.; Warnhoff, E. W. *Can. J. Chem.* **1965**, *43*, 1849. (b) Anderson, W. R., Jr.; Silverstein, R. M. *Anal. Chem.* **1965**, *37*, 1417.

(22) A GLC and 300-MHz ^1H NMR of **9**/**16** gave no indication of isomer ratio.

(23) (a) Klyne, W. "Progress in Stereochemistry"; Butterworths: London, 1954; Vol. 1, pp 40–41 and references therein. (b) Binsch, G. *Top. Stereochem.* **1968**, *3*, 173–174.

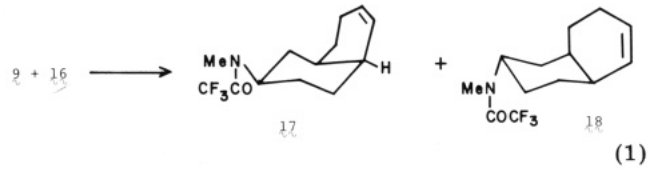
since monosubstituted cis-decalyl derivatives readily adopt that conformation which allows the substituent to be equatorial,[24] it was very probable that **15** would prefer to exist predominantly as its more stable conformer **16**, thus making it more difficult to readily assign stereochemistry to the reductive amination product(s).

The synthesis was thus continued on the assumption that any of the "wrong" isomer **16** would not threaten the planned aminometalation studies (vide supra). The reduction product was subjected to Hegedus' palladium-assisted cyclization method [$PdCl_2(PhCN)_2$, Et_3N, THF]. Although the requisite color changes and deposition of metallic palladium were observed during the course of the reaction, none of the desired product could be detected by either ^1H NMR or mass spectral analysis. A number of subsequent attempts under modified reaction conditions were also uniformly unsuccessful, giving either nonolefinic or olefinic products that could not be spectroscopically correlated with the desired azatricyclic structure **1**.

The amine was also subjected to reaction conditions known to promote intramolecular aminomercuration processes.[10a,d] In every case, only starting material was recovered when **9** (**16**) was exposed to mercuric chloride or mercuric nitrate and then sodium borohydride. The failure of these aminometalation reactions may be due to the possibility that the mercury (or palladium) so strongly coordinates to olefin and amine that it is locked within a cage-type structure, and thus the metal is unable to bond to the proper face of the olefin required for backside attack.[11d]

Since one could also argue that the aminometalation experiments failed because little or none of the desired amine isomer **9** was actually present in our reduction mixture, a shift reagent study was carried out. A series of seven 100-MHz ^1H NMR spectra employing increasing concentrations of the shift reagent Eu-resolve II [Eu-$(C_{10}H_{10}F_7O_2)_3$, Ventron] revealed a 50:50 mixture of **9** and **16** as evidenced by two downfield *N*-methyl absorptions of nearly equal intensity. Thus, the reductive amination process was, in fact, stereochemically indiscriminant.

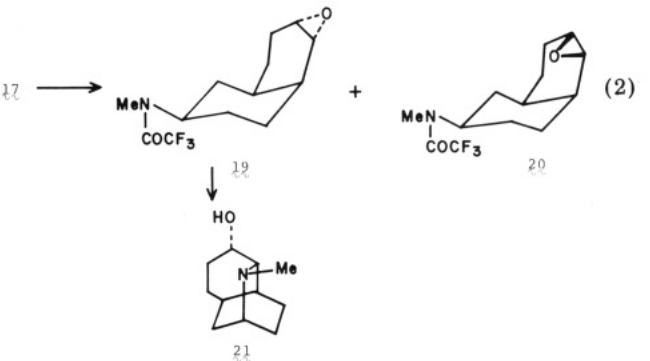
Rather than explore other aminometalation processes, we now elected instead to investigate a somewhat more conventional "epoxide route" to cannivonine. To prevent formation of amine oxide during the epoxidation step, the trifluoroacetyl group was chosen to protect the secondary amine, a choice predicated by the ease of its introduction and, more importantly, by the facility with which it can be removed.[25] An ice-cold mixture of **9**, **16**, and sodium carbonate in an ether–tetrahydrofuran mixture was treated with trifluoroacetic anhydride and stirred vigorously at room temperature. Workup and isolation afforded a high yield of crude material containing two major products as ascertained by thin-layer chromatography. Careful separation of this mixture by MPLC yielded two trifluoroacetamides **17** and **18** (eq 1) in a 60:40 ratio (94% yield), a ratio in fairly good accord with that obtained from the shift reagent experiments.



(1)

Fortunately, inspection of the 250-MHz ^1H NMR spectra for these two amides enabled us to make preliminary assignments of structure. The spectrum of the major isomer presented a single proton absorption (multiplet) at δ 2.4 while that of the minor isomer showed absence of any absorption in the region δ 2.8–2.2. It was our contention that this uniquely shifted proton corresponded to the allylic one (generally δ 2.6) at the ring fusion and, in particular, that it was the one associated with the desired isomer **17**. This proton can assume an equatorial disposition in the correct isomer, whereas in the "wrong" isomer **18** the allylic proton is axially disposed and hence must presumably be buried under the upfield absorptions (above δ 2.2). Thus, not only was the trifluoroacetyl group useful for blocking–deblocking purposes but it also provided an important additional service by anchoring the conformation of **17** and **18**, an effect that was not apparent for the free amine itself. An unambiguous assignment of these trifluoroacetamides and hence a complete analysis of the stereochemistry of the reductive amination process would, however, have to await further chemical transformations.

Treatment of the presumed desired isomer **17** with 2 mol equiv each of 85% *m*-chloroperbenzoic acid and powdered sodium bicarbonate in dry methylene chloride afforded two new products by TLC analysis. Careful separation by MPLC gave a quantitative yield of the two epoxytrifluoroacetamides **19** and **20** in a 70:30 ratio (eq 2). (Reaction of the "undesired" isomer **18** under similar conditions also delivered two epoxides in a 70:30 ratio.) Although the syn-directing effect of an amide group during epoxidation has some precedence,[26] the diminished electron density on the nitrogen atom and the lack of an amide hydrogen in our particular case precluded any chance of binding with the peroxy acid molecule. It was thus postulated that the oxidizing agent attacked **17** predominantly from the least hindered convex side of the molecule to give **19** as the major desired isomer.[27] Not unexpectedly, analysis of the 300-MHz ^1H NMR spectra of these two epoxides did not allow us to make definitive structural assignments. Reaction of isomer **17** with *m*-chloroperbenzoic acid without sodium bicarbonate or with 40% peracetic acid in methylene chloride as solvent under various conditions did not lead to significant differences in the isomer ratio. The final assignment of stereochemistry to these epoxides would thus have to be based on their ability to undergo the transannular ring-opening reaction.



(2)

Treatment of compound **19** with a 7% solution of potassium carbonate in aqueous methanol[25] at reflux temperature for several hours afforded upon workup a single new product by TLC analysis. A 60-MHz ^1H NMR of this material presented one-proton multiplets at δ 3.8 and 2.4, plus an *N*-methyl singlet at δ 2.3. The multiplet at lowest field was noted to fall closely in line with the general shift

(24) Mills, J. A. *J. Chem. Soc.* **1953**, *75*, 260.
(25) Newman, H. *J. Org. Chem.* **1965**, *30*, 1287.
(26) Berti, G. *Top. Stereochem.* **1973**, *7*, 152–153.
(27) Other workers have claimed *exclusive* formation of epoxide **19** from the reaction of **17** with *m*-chloroperbenzoic acid.[8]

Table I. Reduction of the *N*-Methylimine of 10

reducing agent	temp, °C	9, %[a]	16, %[a]
$NaCNBH_3$	rt[b]	60	40
Na-EtOH	reflux	30	70
K-Selectride	0 → rt	33	67
L-Selectride	0 → rt	13	87
L-Selectride	−78 → rt	8	92
$Li(O\text{-}t\text{-}Bu)_3AlH$	−78 → rt	57	43

[a] The percentage values represent relative GLC peak areas of the trifluoroacetyl derivatives of 9 and 16 (i.e., 17 and 18). See the Experimental Section for a description of the column and conditions. [b] Room temperature.

position of a methinyl proton adjacent to an alcohol. The infrared spectrum displayed a very strong hydroxyl absorption at 3350 cm^{-1}. The mass spectrum revealed a base peak at 181 corresponding to the desired azatricyclic alcohol **21**. In addition, a peak of very low intensity was present at m/e 199, a value that corresponded to the net addition of water to the amino epoxide **19**. In order to obtain further chemical evidence for **21**, it was treated with an excess of sodium acetate and acetic anhydride in boiling methylene chloride for 5 h. On workup, a new product was isolated whose ^1H NMR showed two methyl singlets at δ 2.3 and 1.9. An IR spectrum indicated absorption at 1740 cm^{-1} and the absence of any above 3000 cm^{-1}, while the mass spectrum gave a base (and parent) peak of 223 (181 plus CH_2CO) corresponding to the acetate derivative of **21**. The above evidence coupled with the acquisition of a ^{13}C NMR and comparison with spectral data supplied by Professor D. Evans firmly established that we had indeed generated the desired azatricycle. The transannular cyclization process thus proved to be an extremely efficient and effective method for creating the cannivonine skeleton. Latter in our studies, it was in fact discovered that by simply stirring **19** at *room temperature* overnight with a 7% solution of potassium carbonate in aqueous methanol, **21** could be obtained as the exclusive product.[28]

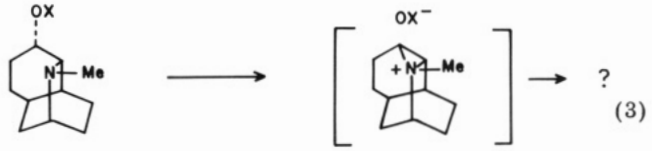
With **21** in hand, our initial structural assignments for the trifluoroacetamides **17** and **18** and the epoxides **19** and **20** were now secured. This information thus made it possible for us to reexamine the reductive amination reaction of **10** with the hope of improving its stereoselectivity. Since the use of other reducing agents demanded prior formation and isolation of the imine (**22**, **23**), an examination of a few of the available literature methods for imine preparation was made.[29] The most expeditious method found consisted of warming **10** and excess methylamine in benzene containing magnesium sulfate at 40 °C for several hours. Filtration under an argon blanket followed by concentration gave the crude imine, which was used without further purification.

22 23

Reduction of this imine with several selected reducing agents was then examined. The results of this study are summarized in Table I. If the results of the three Selectride experiments (increasing amounts of the "wrong" isomer **16**) can be rationalized on the basis of the unique propensity of these reagents for equatorial attack,[30] then the transition state for reduction must look more like conformation **22** than **23**. The lithium tri-*tert*-butoxyaluminum hydride result is in line with such a conformational preference, for predominant axial attack is generally observed with this reagent in the absence of a C3 or C5 axial substituent.[31] Thus, if the transition state involved a conformation resembling **23**, a much higher percentage of **16** would have been expected with $Li(O\text{-}t\text{-}Bu)_3AlH$ due to the substantial steric interference from the C3 axial substituent. The isomer ratio observed for the sodium–ethanol reduction is less readily rationalized. Perhaps the fact that this reduction was run at reflux temperatures is of some significance.[32]

Although the foregoing reduction study was certainly not exhaustive, the prospect of increasing the percentage of **9** (and thus **17**) did not look promising. It was thus considered fortunate that the convenient in situ sodium cyanoborohydride reduction of **13** proceeded in very good yield (>90%). The Borch procedure was unquestionably the method of choice for our synthesis.[33] Having satisfactorily answered the stereochemical questions that evolved during this study, the final problem of converting intermediate **21** into the target structure **1** could now be addressed.

Although the literature abounds with procedures for dehydration of alcohols and their derivatives, skeletal reorganization as a consequence of intramolecular displacement of any potentially eliminateable group by the nitrogen atom of **24** (eq 3) with aziridinium ion formation was deemed a potential side reaction. This possibility (eq 3) thus required that particular caution be exercised in the execution of this final step.



(3)

24, X = activating group

25, X = $\overset{\overset{S}{\|}}{C}SMe$

26

(28) Other workers have claimed the isolation of the amino epoxide precursor to amino alcohol **21** from treatment of the trifluoroacetamide **19** under identical conditions.[8]

(29) (a) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (b) Meister, W.; Guthrie, R. D.; Maxwell, J. L.; Jaeger, D. A.; Cram, D. J. *Ibid.* **1969**, *91*, 4452. (c) Fry, A.; Reed, R. *Ibid.* **1969**, *91*, 6448. (d) Kyba, E. P. *Org. Prep. Proc. Int.* **1970**, *2*, 149.

(30) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. (b) Brown, C. A. *Ibid.* **1973**, *95*, 4100. An empirical force-field calculation carried out using Allinger's MM2 program on ketone **10** reveals a very small energy difference (~0.7 kcal) between the two conformers. Thus, in accord with the Curtin–Hammett principle, the product ratios in the reduction of **22**/**23** do not reflect conformational populations. We thank Mr. Frank Brown for carrying out these calculations.

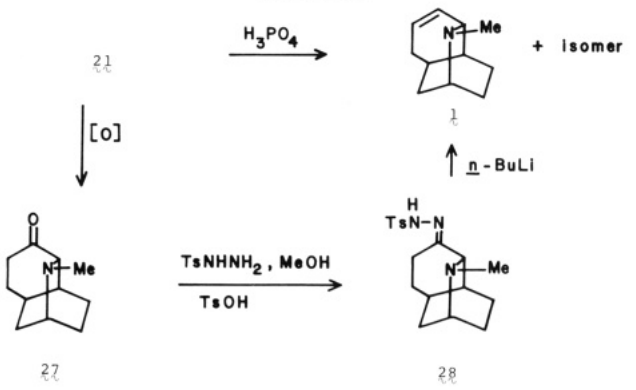
(31) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: New York, 1972; pp 62–64.

(32) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: New York, 1972; pp 152–153.

(33) A major contradiction exists between our reduction study and that of Professor Evans.[8] Evans claimed that reduction of the *N*-methylimine of **10** with L-Selectride afforded a greater than 99:1 ratio of **9** to **16**, a result directly opposite to ours (8:92). The olefinic absorption in the ^1H NMR of Evans' reduction product was identical (a broad singlet) with that which we observed for the "wrong" amine isomer **16** (obtained in pure form by removing the trifluoroacetyl group of **18**). The olefinic protons for **9** and **17** appear as a series of four broad peaks. Moreover, we found that the methinyl ring carbon α to the amino group in **16** had precisely the same ^{13}C NMR chemical shift as that reported for their reduction product. Since they were able to convert their L-Selectride reduction product into the amino alcohol **21**, we assume that epimerization at C2 must have occurred during their Al_2O_3-promoted transannular cyclization reaction. Aluminum oxide is known to epimerize alcohols, thus providing some foundation for such an assumption.[34]

(34) Doering, W. von E.; Aschner, T. C. *J. Am. Chem. Soc.* **1949**, *71*, 838.

Scheme III



Standard dehydration procedures (i.e., MsCl–DBU[35] and $POCl_3$–pyridine[36]) were studied first. Both of these experiments yielded, however, the same nonolefinic product which differed in its 60-MHz ^1H NMR from starting material (one-proton multiplet at δ 4.0 vs. 3.8 for **21**). Attempted cis elimination of the xanthate **25** in Decalin at 190 °C resulted in recovery of starting material.[37] Treatment of the amino alcohol **21** in hot dimethyl sulfoxide also failed, giving nonolefinic products.[38] Contrastingly, on heating the alcohol in HMPT[39] at 215 °C for several hours, material displaying olefinic absorption in its 60-MHz ^1H NMR (m, δ 5.4–6.1) was obtained. Unfortunately, many attempts (even VPC) to isolate the olefin product free of HMPT-derived byproducts were unsuccessful.

Since the aforementioned aziridinium ion species **26** was suspected to be the origin of the problem in the dehydration attempts, a species that might, of course, be generated even during derivatization of the alcohol, it was reasoned that reaction in an acidic medium would inactivate the nitrogen and thus increase the likelihood for olefin formation without rearrangement. Treatment of **21** (Scheme III) with hot (195 °C) phosphoric acid[40] for 2 h followed by basification and continuous extraction with ether afforded a two-component mixture (~1:1 by TLC) whose 100-MHz ^1H NMR presented substantial olefinic absorption. The more polar of the carefully separated products gave the correct molecular ion for the target structure **1**. The key peak positions in its 100-MHz ^1H NMR, however, compared poorly with the 60-MHz ^1H NMR data published by Jankowski for cannivonine. The less polar compound likewise displayed the correct parent ion in its mass spectrum and olefinic absorption in its NMR spectrum. Again, however, these NMR data failed to match those reported for cannivonine.

Since we were unable to procure an authentic sample of cannivonine, we were obligated to develop yet another route to **1** from amino alcohol **21** in order to unambiguously establish the outcome of the phosphoric acid dehydration experiment. The Shapiro tosylhydrazone olefination method[41] was chosen as a "mild" alternative. Thus, oxidation of our amino alcohol with Jones reagent in acetone or with pyridinium chlorochromate in methylene chloride afforded the ketone **27** (IR 1720 cm^{-1}), which was converted without purification into its tosylhydrazone **28** (IR 3320, 1680, 1160 cm^{-1}). Decomposition of **28** with *n*-butyllithium afforded an amine product whose R_f value was identical with that of the more polar amine isolated from the phosphoric acid reaction. The 100-MHz ^1H NMR, ^{13}C NMR, and mass spectral data for these two independently prepared amines were fully in accordance and, in addition, were identical with the spectral data for compound **1** kindly provided by Professor D. Evans.

This unambiguous ten-step synthesis of **1** and its spectral nonidentity with the data reported for cannivonine lead us to conclude that a definite structural misassignment has been made. The structural assignments for the other cannivonines may also be in jeopardy. A complete reinterpretation of the published data (and probably reisolation as well) and a reassignment of these structures appear to be in order.[42]

Experimental Section

General Methods. Melting points were determined on either a Fisher-Johns or Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer 247 or 700 infrared spectrophotometer using the polystyrene absorption at 1601 cm^{-1} as a reference. The ^1H NMR spectra were recorded on a JEOL JNM-MH-100, Bruker WH-300, or HF-250 (NIH NMR Facility for Biomedical Studies, Mellon Institute) NMR spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as solvent. The ^{13}C NMR spectra were recorded on a JEOL JNM-FX60 Fourier transform NMR spectrometer using $CDCl_3$ as solvent and internal reference. Low-resolution mass spectra were obtained on a LKB 9000A gas chromatograph–mass spectrometer. High-resolution mass spectra were obtained on a Varian MAT CH-5DF mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed by using either Brinkmann precoated plastic sheets (silica gel without gypsum, 0.25 mm, with fluorescent indicator UV_{254}) or Merck precoated glass plates (aluminum oxide F-254, type T). Developed plates were visualized by staining with either a solution of phosphomolybdic acid in ethanol or Dragendorff's reagent. Medium-pressure liquid chromatography was performed by using Woelm silica gel (particle size 32–63 μm) and redistilled ethyl acetate and hexanes. Gas–liquid chromatography was performed on a Varian Aerograph (Model 90-P) instrument with helium as carrier gas. Pyridine and dimethoxyethane were dried by distillation from calcium hydride. Ethanol-free chloroform and dry methylene chloride were obtained by passage through a column of neutral alumina. Diethyl ether and tetrahydrofuran were dried by distillation from sodium benzophenone ketyl. All other solvents were used as commercially obtained. Reactions were conducted under an argon atmosphere (balloon filled) unless stated otherwise or when dry conditions were unnecessary. "Concentration" implies the removal of volatiles at the aspirator. "Workup" means that explicit detail can be found in the literature preparation.

Experimental Procedures. 5-Cyanobicyclo[2.2.2]oct-2-ene. A mixture of freshly distilled acrylonitrile (4.25 g, 80.0 mmol), 1,3-cyclohexadiene (3.21 g, 40.0 mmol), and hydroquinone (0.05 g, 0.5 mmol) was sealed in a Pyrex tube and heated at 120 °C for 18 h. The resulting mixture was concentrated and distilled (85–90 °C (3 mmHg) bath temperature) to give 4.30 g (81%) of the nitrile as a white semisolid: IR ($CHCl_3$) 2225, 1460, 1445, 1370, 835 cm^{-1}; ^1H NMR (300 MHz) δ 6.50–6.22 (four ddd, 2 H, J = 7.3, 7.3, 1.2 Hz), 2.92–2.41 (m, 3 H), 2.09–1.92 (m, 1 H), 1.77–1.22 (m, 5 H); MS (15 eV), m/e 133 (M^+), 110, 105, 80 (base). Exact mass calcd for $C_9H_{11}N$ 133.089, found 133.088.

5-Chloro-5-cyanobicyclo[2.2.2]oct-2-ene. To a refluxing mixture of pyridine (2.60 g, 0.33 mol), phosphorus pentachloride (52.0 g, 0.25 mol), and 50 mL of chloroform was added dropwise

(35) Harrison, I.; Harrison, S. "Compendium of Organic Synthetic Methods"; Wiley-Interscience: New York, 1971; Vol. 1, p 485.
(36) Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 878–879.
(37) Harrison, I.; Harrison, S. "Compendium of Organic Synthetic Methods"; Wiley-Interscience: New York, 1971; Vol. 1, p 487.
(38) Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 301–302.
(39) (a) Monson, R. *Tetrahedron Lett.* **1971**, 567. (b) Monson, R.; Priest, D. *J. Org. Chem.* **1971**, *36*, 3826.
(40) (a) Dehn, W. M.; Jackson, K. E. *J. Am. Chem. Soc.* **1933**, *55*, 4284. (b) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1952**, 1430.
(41) Shapiro, R. H.; Heath, M. *J. Am. Chem. Soc.* **1967**, *89*, 5734.
(42) Professor K. Jankowski has apparently also expressed some concern about the correctness of his structural assignment to cannivonine in several IUPAC lectures (Ottawa, 1974, and Tokyo, 1977).

over 3 h a solution of the above nitrile (21.3 g, 0.16 mol) in 100 mL of chloroform. The resulting mixture was heated at reflux for 13 h, cooled, and poured onto ice. The residue obtained after workup was distilled (95–100 °C (2 mmHg) bath temperature) to give 25.1 g (93%) of the title compound as a white semisolid: IR ($CHCl_3$) 2225, 1460, 1440, 1365, 960 cm^{-1}; ^1H NMR (300 MHz) δ 6.53–6.22 (m, 2 H), 3.15–3.04 (m, 1 H), 2.75–2.71 (m, 1 H), 2.54–2.01 (m, 3 H), 1.70–1.26 (m, 3 H); MS (15 eV), *m/e* 169, 167 (M^+), 132, 104, 80 (base). Exact mass calcd for $C_9H_{10}ClN$ 167.050, found 167.050.

Bicyclo[2.2.2]oct-5-en-2-one (12). To a stirred solution of the α-chloronitrile (11.1 g, 67.0 mmol) in 100 mL of dimethyl sulfoxide was added portionwise a slurry of 85% potassium hydroxide (17.7 g, 316.0 mmol) in 6 mL of water. The resulting mixture was stirred at room temperature for 13.5 h. The residue obtained after workup was distilled (95–100 °C (13 mmHg) bath temperature) to give 6.63 g (82%) of **12** as a white semisolid: IR ($CHCl_3$) 3050, 1710, 1605, 1400, 1355, 1090, 850 cm^{-1}; ^1H NMR (300 MHz) δ 6.49 (ddd, 1 H, J = 7.3, 7.3, 1.0 Hz), 6.21 (ddd, 1 H, J = 7.3, 7.3, 1.6 Hz), 3.14 (m, 1 H), 3.00 (m, 1 H), 2.04 (m, 2 H), 1.91–1.47 (m, 4 H); MS (15 eV), *m/e* 122 (M^+), 80 (base). Exact mass calcd for $C_8H_{10}O$ 122.073, found 122.073.

2-Ethenylbicyclo[2.2.2]oct-5-en-2-ol (11). To 15 mL of a 1.50 M solution of vinylmagnesium bromide in tetrahydrofuran at room temperature was added dropwise a solution of **12** (2.33 g, 19.0 mmol) in 40 mL of tetrahydrofuran. After stirring at room temperature for 15 min, the mixture was heated at reflux for 15 min, cooled to 0 °C, quenched with saturated ammonium chloride, and extracted with petroleum ether. The crude oil obtained was distilled (85–87 °C (9 mmHg) bath temperature) to give 2.40 g (84%) of a 2:1 mixture (separable by chromatography on silica gel with 10% ethyl acetate–hexanes as eluent) of **11** and its isomer as a colorless oil: IR (neat) 3400, 3080, 3050, 1635, 1370, 1140, 990, 920, 870 cm^{-1}; ^1H NMR (for **11**, 300 MHz) δ 6.23 (m, 2 H), 5.91 (dd, 1 H, J = 17.3, 10.7 Hz), 5.12 (dd, 1 H, J = 17.3, 1.3 Hz), 4.92 (dd, 1 H, J = 10.7, 1.3 Hz), 2.61 (m, 1 H), 2.38 (m, 1 H), 2.19 (m, 1 H), 1.73–1.61 (m, 2 H), 1.48 (dd, 1 H, J = 13.3, 2.3 Hz), 1.41 (s, 1 H), 1.36–1.05 (m, 2 H); ^1H NMR (for the endo alcohol, 300 MHz) δ 6.46 (ddd, 1 H, J = 7.3, 7.3, 0.9 Hz), 6.29 (ddd, 1 H, J = 7.3, 7.3, 1.0 Hz), 6.04 (dd, 1 H, J = 17.3, 10.8 Hz), 5.34 (dd, 1 H, J = 17.3, 1.3 Hz), 5.13 (dd, 1 H, J = 10.8, 1.3 Hz), 2.66 (m, 1 H), 2.53 (m, 1 H), 1.87 (dd, 1 H, J = 13.7, 2.2 Hz), 1.75 (s, 1 H), 1.70–1.62 (m, 1 H), 1.45–1.10 (m, 4 H); MS (15 eV), *m/e* 150 (M^+), 132, 96, 92, 80 (base). Exact mass calcd for $C_{10}H_{14}O$ 150.104, found 150.104.

***cis*-3,4,4a,7,8,8a-Hexahydro-2(1*H*)-naphthalenone (10).** A 24% potassium hydride suspension in oil (9.50 g, 2.28 g of KH, 57.0 mmol) was washed with ether (3×) and diluted with 8 mL of dimethoxyethane. To the oil-free KH was then added dropwise a solution of the 2:1 mixture of the above alcohols (4.00 g, 27.0 mmol) in 15 mL of dimethoxyethane, followed by addition of a solution of 18-crown-6 (8.20 g, 31.0 mmol) in 25 mL of dimethoxyethane. The resulting dark mixture was stirred at room temperature for 14 h, quenched with ethanol and saturated ammonium chloride, and extracted with ether. The resulting orange oil was subjected to medium-pressure liquid chromatography, employing 7% ethyl acetate–hexanes as eluent, to give 2.25 g (85%) of **10** as a colorless oil: IR (neat) 3020, 1710, 1645, 1430 cm^{-1}; GLC (7 ft × 0.25 in. aluminum column; 15% SE-30 on 60/80 AW DMCS Chrom P; 190 °C, He flow of 54 mL/min) R_t 6 min; ^1H NMR (300 MHz) δ 5.79–5.72 (m, 1 H), 5.65–5.59 (m, 1 H), 2.52 (br m, 1 H), 2.38–2.21 (m, 5 H), 2.11–1.50 (m, 6 H); MS (70 eV), *m/e* 150 (M^+), 132, 108, 93, 80 (base), 67, 39, 27. Exact mass calcd for $C_{10}H_{14}O$ 150.104, found 150.104.

(2β,4aα,8aα)-1,2,3,4,4a,7,8,8a-Octahydro-*N*-methyl-2-naphthalenamine (9, 16). To a stirred solution of monomethylamine hydrochloride (7.80 g, 117.0 mmol) in 60 mL of absolute methanol were added successively a solution of **10** (1.75 g, 11.7 mmol) in 20 mL of absolute methanol and a solution of sodium cyanoborohydride (0.60 g, 9.30 mmol) in 20 mL of absolute methanol. The resulting mixture was stirred at room temperature for 24 h, made acidic (pH ~2) with 6 N HCl, and concentrated. The residue was diluted with 3 mL of water and extracted with ether (2×). The organic layers were combined and washed once with 3 N HCl. The aqueous layers were combined, made basic (pH ~12) with solid KOH, and extracted with ether (4×). These latter ether layers were then combined, washed once with brine, and dried over $MgSO_4$. Filtration and concentration gave 1.77 g (92%) of **9/16** as a pale yellow oil: IR (neat) 3300, 3015, 1650, 1475, 1450, 1125, 1000, 860, 750, 725, 690 cm^{-1}; ^1H NMR (300 MHz) δ 5.62 (m, 2 H), 2.48 (tt, 1 H, J = 10.6, 3.6 Hz), 2.42 (s, 3 H), 2.10–0.90 (m, 13 H); MS (15 eV), *m/e* 165 (M^+, base), 122, 109, 83, 71, 70, 57; GLC (5 ft × 0.25 in. aluminum column; 28% Pennwalt–4% KOH on Gas Chrom R; 190 °C, He flow of 54 mL/min) R_t 15.0 min. Exact mass calcd for $C_{11}H_{19}N$ 165.152, found 165.152.

(2α,4aβ,8aβ)-2,2,2-Trifluoro-*N*-methyl-*N*-(1,2,3,4,4a,7,8,8a-octahydro-2-naphthalenyl)acetamide (17). To an ice-cooled vigorously stirred solution–suspension of **9/16** (1.77 g, 10.7 mmol) and sodium carbonate (5.50 g, 51.9 mmol) in a mixture of ether and tetrahydrofuran (56 mL:14 mL) was added quickly trifluoroacetic anhydride (5.2 mL, 36.0 mmol). The ice bath was removed and the mixture stirred for 30 min. Chloroform (30 mL) was added in one portion followed by 20 mL of water. The organic layer was washed with water (2×) and brine (1×). The aqueous layers were combined and extracted with ether (1×). The organic layers were dried over $MgSO_4$ and concentrated to give a pale orange oil. The oil was purified by medium-pressure liquid chromatography, with 5% ethyl acetate–hexanes as eluent to give 1.58 g (56%) of **17** as a white solid: mp 68.5–69.5 °C (hexanes); IR ($CHCl_3$) 1670, 1440, 1410, 1180, 1140, 1075 cm^{-1}; ^1H NMR (300 MHz) δ 5.75–5.67 (m, 1 H), 5.41–5.32 (m, 1 H), 4.45–4.30, 3.82–3.70 (m, 1 H), 2.93, 2.87 (q and s, 3 H), 2.40 (br s, 1 H), 2.08–1.30 (m, 11 H); MS (15 eV), *m/e* 261 (M^+), 192, 134 (base), 92; GLC (10 ft × 0.25 in. aluminum column, 15% Carbowax 20M on 60/80 AW Chrom P; 200 °C, He flow 54 mL/min) R_t 15.7 min. Anal. Calcd for $C_{13}H_{18}F_3NO$: C, 59.74; H, 6.95; N, 5.36; F, 21.83. Found: C, 59.67; H, 6.90; N, 5.25; F, 21.72. Also obtained was 1.05 g (38%) of **18** as a clear oil: ^1H NMR (250 MHz) δ 5.56 (br s, 2 H), 4.40, 3.92 (m, 1 H), 2.93, 2.83 (q and s, 3 H), 2.12–1.28 (m, 12 H); GLC R_t 18.7 min.

(1aα,3aα,5β,7aα,7bα)-*N*-(Decahydronaphth[1,2-*b*]oxiren-5-yl)-2,2,2-trifluoro-*N*-methylacetamide (19). To a stirred ice-cooled solution–suspension of *m*-chloroperbenzoic acid (1.52 g, 8.80 mmol) and sodium bicarbonate (0.75 g, 8.80 mmol) in 80 mL of methylene chloride was added a solution of **17** (1.15 g, 4.40 mmol) in 20 mL of methylene chloride. The resulting mixture was stirred at room temperature for 15 h, cooled to 0 °C, quenched with saturated aqueous solutions of sodium bisulfite and sodium bicarbonate, and diluted with ether. The organic layer was collected, the aqueous phase was extracted with ether (2×), and the organics were combined, washed with saturated sodium bicarbonate (1×) and brine (1×), and dried over $MgSO_4$. The residue obtained was subjected to medium-pressure liquid chromatography, with 20% ethyl acetate–hexanes as eluent to give 0.854 g (70%) of **19** as a white solid: mp 58–61 °C (hexanes); IR ($CHCl_3$) 1675, 1445, 1140, 1080, 915, 830 cm^{-1}; ^1H NMR (300 MHz) δ 4.31 (tt, 0.5 H, J = 12.0, 3.6 Hz), 3.76 (br t, 0.5 H), 3.23 (br s, 1 H), 2.99, 2.92 (q and s, 3 H), 2.85 (br s, 1 H), 2.07–1.26 (m, 12 H); MS (15 eV), *m/e* 277 (M^+), 208, 150 (base), 132, 85. Anal. Calcd for $C_{13}H_{18}F_3NO_2$: C, 56.29; H, 6.55; N, 5.05; F, 20.57. Found: C, 56.40; H, 6.58; N, 4.98; F, 20.69. Also obtained was 0.366 g (30%) of **20** as a white solid: mp 74–76 °C (hexanes); ^1H NMR (300 MHz) δ 4.40 (tt, 0.5 H, J = 12.0, 4.0 Hz), 3.76 (br t, 0.5 H), 3.11 (m, 1 H), 3.05 (m, 1 H), 2.99, 2.93 (q and s, 3 H), 2.30–1.20 (m, 12 H).

(1α,2β,4aβ,6α,8aβ)-Decahydro-9-methylnaphthalen-1,6-imin-2-ol (21). A solution of **19** (1.108 g, 4.00 mmol) and potassium carbonate (4.30 g, 31.0 mmol) in 110 mL of methanol was brought to reflux with rapid stirring. After 5 min, 2.6 mL of water was added and the resulting mixture refluxed for an additional 2 h. The mixture was cooled and diluted with water, and the methanol was removed in vacuo. The aqueous residue was extracted with ether (4×), and the organics were combined, washed with brine, and dried over $MgSO_4$. The yellow oil obtained by rotary evaporation was bulb-to-bulb distilled (107–115 °C (0.08 mmHg) oven temperature) to give 0.662 g (91%) of **21** as a white solid: mp 80–81.5 °C (hexanes); IR ($CHCl_3$) 3600, 2920, 1450, 1150, 1080, 1000 cm^{-1}; ^1H NMR (300 MHz) δ 3.75 (m, 1 H), 2.56 (m, 1 H), 2.37 (s, 3 H), 2.26 (m, 1 H), 2.23–2.13 (m, 1 H), 2.07–1.93 (m, 1 H), 1.85–1.15 (m, 11 H); MS (70 eV), *m/e* 181 (M^+), 122, 96; ^{13}C NMR ($CHCl_3$) δ 69.20 (d), 65.33 (d), 51.37 (d), 42.87 (q),

33.35 (t), 28.79 (d), 26.50 (d), 26.33 (t), 24.98 (t), 23.75 (t), 18.63 (t). Anal. Calcd for $C_{11}H_{19}NO$: C, 72.87; H, 10.57; N, 7.73. Found: C, 73.00; H, 10.73; N, 7.68.

1,4,4a,5,6,7,8,8a-Octahydro-9-methylnaphthalen-1,6-imine (1). Procedure A. A mixture of **21** (0.020 g, 0.11 mmol) and 85% phosphoric acid (0.4 mL) was heated at 195 °C for 2 h. The mixture was cooled, made basic with a 50% aqueous solution of potassium hydroxide, and extracted with ether (4×). The organics were combined, washed with brine, and dried over $MgSO_4$. The crude product was chromatographed on basic alumina (Merck, type T), with a mixture of chloroform, cyclohexane, and diethylamine (1:1:0.03) as eluent to give 4.0 mg (22%) of **1** as a pale yellow oil: IR (neat) 3050, 1650, 1455, 1360, 1240, 1165, 1150, 1015 cm^{-1}; ^1H NMR (100 MHz) δ 6.1–5.85 (m, 1 H), 5.75–5.50 (m, 1 H), 2.80 (m, 1 H), 2.58 (m, 1 H), 2.46 (s, 3 H), 2.40–1.10 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 130.86, 126.05, 56.53, 46.64, 41.71, 33.92, 29.89, 26.64, 23.78, 19.62; MS (15 eV), *m/e* 163 (M^+, base), 148, 134, 129, 122, 94. Exact mass calcd for $C_{11}H_{17}N$ 163.136, found 163.136.

Procedure B. To an ice-cooled solution of **21** (0.30 g, 1.66 mmol) in 16 mL of acetone was added Jones reagent until an orange color persisted. The resulting mixture was stirred at room temperature for 1 h, excess Jones reagent destroyed by addition of isopropanol, and the green mixture made basic with a 5% aqueous solution of sodium hydroxide. The solution was decanted and concentrated and the residue extracted with a mixture of ether and methylene chloride (4×). The organic layers were combined, washed once with brine, and dried over $MgSO_4$. The azaundecanone **27** was obtained as a pale yellow oil and was used without further purification; IR (neat) 1710 cm^{-1}; ^1H NMR (100 MHz) δ 3.26 (m, 1 H), 2.62 (br s, 2 H), 2.33 (s, 3 H), 2.20–1.10 (br m, 11 H).

A solution of **27** (0.265 g, 1.48 mmol) and *p*-toluenesulfonohydrazide (0.28 g, 1.50 mmol) in 4 mL of methanol was stirred at room temperature for 36 h. The mixture was concentrated, and the resulting solid residue was chromatographed on silica gel with a mixture of chloroform and methanol (10:1) as eluent to give 0.50 g of **28** as an amorphous white solid: IR ($CHCl_3$) 3320, 1680, 1610, 1455, 1385, 1340, 1160, 1085, 1010, 900 cm^{-1}; ^1H NMR (100 MHz) δ 7.80 (d, 2 H), 7.25 (d, 2 H), 2.72 (m, 1 H), 2.48 (m, 1 H), 2.37 (s, 3 H), 2.07 (s, 3 H), 2.3–1.0 (m, 12 H); MS (15 eV), *m/e* 348, 347 (M^+), 278, 226, 192, 177 (base), 91.

To a stirred solution of the hydrazone **28** in 75 mL of tetrahydrofuran at −78 °C was added 3.8 mL (4 equiv) of a 1.6 M hexane solution of *n*-butyllithium over a 3-min period. The resulting orange solution was allowed to gradually reach room temperature and then stirred for 1.5 h. The mixture was quenched with methanol and concentrated, the residue diluted with water, and the aqueous solution extracted with a mixture of ether and methylene chloride (4×). The extracts were combined, washed once with brine and dried over $MgSO_4$. The brown oil obtained on rotary evaporation was subjected to preparative TLC (aluminum oxide, F-254, Merck type T), employing a mixture of chloroform, cyclohexane, and diethylamine (1:1:0.03) as the developing solvent to give 0.045 g (17% overall from **21**) of **1** as a pale yellow oil: ^1H NMR (250 MHz) δ 5.96 (m, 1 H), 5.69 (m, 1 H), 2.89 (m, 1 H), 2.62 (m, 1 H), 2.47 (s, 3 H), 2.40–1.20 (m, 10 H). The 100-MHz ^1H NMR, ^{13}C NMR, IR, MS, and TLC R_f of this material were found to be identical with those obtained for the sample prepared by procedure A.

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Registry No. **1**, 84694-66-6; **9**, 84694-63-3; **10**, 936-37-8; **10** *N*-methylimine, 84694-69-9; **11** (isomer 1), 768-77-4; **11** (isomer 2), 768-78-5; **12**, 2220-40-8; **16**, 84694-64-4; **17**, 84694-65-5; **19**, 84773-35-3; **20**, 84773-37-5; **21**, 84773-36-4; **27**, 84694-68-8; **28**, 84694-67-7; 5-cyanobicyclo[2.2.2]oct-2-ene, 38258-93-4; 5-chloro-5-cyanobicylo[2.2.2]oct-2-ene, 6962-73-8; acrylonitrile, 107-13-1; 1,3-cyclohexadiene, 592-57-4; vinyl bromide, 593-60-2; *p*-tolylsulfonylhydrazine, 1576-35-8.

Synthesis of 4-Fluoroestradiol Analogues

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The synthesis of several 4-fluoro analogues of estradiol is described.

For ongoing studies of the noninvasive differentiation of hormone-dependent from hormone-independent mammary tumors[1-5] we have prepared several 4-fluorinated analogues of estradiol, the syntheses of which are the subject of this paper. Results of the biological studies will be published elsewhere.

The required 4-fluoroestradiol (**4**, Chart I) was prepared from 19-nortestosterone (**1**) via enamine **2** and 4-fluoro-19-nortestosterone (**3**), as described by Joly and Warnant.[6] Jones' oxidation of **4** gave 4-fluoroestrone (**5a**), which on treatment with isopropenyl acetate in the presence of catalytic amounts of H_2SO_4, gave the expected 4-fluoroestrone enol diacetate (**6b**). Bromine was allowed to react with **6b** in the presence of potassium carbonate to yield 4-fluoro-16α-bromoestrone acetate (**7**) in excellent yield. Reduction of 4-fluoro-16α-bromoestrone acetate (**7**) with sodium borohydride in ethanol at 4 °C gave 4-fluoroestradiol (**4**, 15%) and the isomeric bromo alcohols 4-fluoro-16α-bromo-3,17β-diol **8a** (51%) and 4-fluoro-16a-bromo-3,17α-diol **8b** (30%). We have previously reported similar results for the reduction of 16-bromoestrone-3-acetate.[3]

Equilibration of 4-fluoro-16α-bromoestra-1,3,5(10)-triene-3,17β-diol (**8a**) with sodium iodide in ethyl methyl ketone under reflux for 24 h gave the 4-fluoro-16α-iodoestra-3,17β-diol (**9**, δ 0.75 (18-H)). The retention of configuration at C-16 is presumably the result of the neighboring group participation.[2,3]

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